wherein X_1 and X_3 may be the same or different and each is an amino acid sequence consisting of from 0 to 40 naturally occurring amino acid residues; X_2 is any amino acid sequence of from 10 to 13 residues derived from or contiguous within amino acids 506 to 518 inclusive of human GAD65 or amino acids 24 to 36 inclusive of human proinsulin; and wherein said peptide is capable of reacting with T cells and modifying T-cell function when incubated with cells from subjects with pre-clinical or clinical Insulin-Dependent Diabetes Mellitus (IDDM).

Please amend claim 42 as follows:

42.(Twice Amended) A method of treatment comprising administering to a subject an effective amount of a peptide for a time and under conditions sufficient to remove or substantially reduce the presence in said subject of autoreactive T-cells or auto antibodies to IDDM autoantigens wherein the peptide consists of the formula:

$$X_1 X_2 X_3$$

wherein X_1 and X_3 may be the same or different and each is an amino acid sequence consisting of from 0 to 40 naturally occurring amino acid residues; X_2 is any amino acid sequence of from 10 to 13 residues derived from or contiguous within amino acids 506 to 518 inclusive of human GAD65 or amino acids 24 to 36 inclusive of human proinsulin; and wherein said peptide is capable of reacting with T cells and modifying T-cell function when incubated with cells from subjects with pre-clinical or clinical Insulin-Dependent Diabetes Mellitus (IDDM).

REMARKS

In the Official Action dated October 25, 2001, claims 39, 40, 42 and 43 have been rejected under 35 U.S.C. 112, first paragraph as allegedly lacking enabling support.

Claims 39 and 42 have been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite.

This response addresses each of the Examiner's rejections. Accordingly, the present application is condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claims 39, 40, 42 and 43 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support. The Examiner specifically alleges that the specification "fails to establish any connection between the claimed peptides' ability to cause T-cells to proliferate *in vitro* and an ability to provide an effective treatment for IDDM." The Examiner further alleges that "given the huge ranges of the T-cells proliferative responses...and the fact that the peptides cause proliferation in some control experiments while failing to cause proliferation in some of the experiments using IDDM-at risk T-cells, it appears the instant data must be considered non-conclusive."

Applicants respectfully submit that the pending claims are fully enabled in accordance with the provisions of 35 U.S.C. §112, first paragraph. Applicants submit that the present specification identifies sequences from human proinsulin, e.g. SEQ ID NO:1 that have similarity with a sequence from Glutamic Acid Decarboxylase (GAD), which was identified as stimulating peripheral blood T-cell proliferative and cytokine responses in humans at-risk for Insulin-Dependent Diabetes Mellitus. Inasmuch as these proinsulin sequences are demonstrated to function as T-cell epitopes in humans at-risk of IDDM, the present invention discloses and enables the sequences, modifications and applications for diagnostic and/or therapeutic purposes in IDDM. In effect, any protein, peptide or auto-antigen demonstrated to be recognized by T-cells from individuals at-risk for an autoimmune disease, is not only a

target but also a potential immunotherapeutic tool. The Examiner's attention is respectfully directed to the article by Harrison and Hafler entitled "Antigen-Specific Therapy for Autoimmune Disease" in Current Opinions in Immunology 12:704-711, 2000, (attached as Exhibit A) which confirms that peptide autoantigens such as those identified by the present inventors are immunotherapeutic tools.

The Examiner's statement that the "instant data must be considered non-conclusive" because of the "huge ranges of T-cells proliferative responses" and that the notion that the peptides cause proliferation in some controls while failing to cause proliferation in some at-risk subjects, is incorrect. T-cell proliferative responses are well-known to vary greatly between individuals depending on factors such as the precursor frequency of antigen-specific T-cells, the number of assay replicates, HLA allele types and the stage of disease. The statistical treatment summarizing the results achieved in accordance with the present invention, clearly demonstrates that despite large variances, differences between IDDM at-risk and control subjects were significant. This conclusion is irrefutable. When responses were "corrected" for basal proliferation, the resultant delta values revealed that reactivity to the proinsulin sequence was confined to the at-risk subjects. Moreover, it is reasonable that T-cells from some disease subjects will fail to respond to auto-antigen protein or peptide, whereas some HLA-matched control subjects will respond. It is now widely accepted that self/non-self discrimination is not absolute and that T-cell auto-reactivity is present in normal individuals.

The Examiner further alleges that "while working examples cannot be required, the induction of specific tolerance is highly complex and unpredictable, thus requiring enablement..." Applicants submit that the art is replete with considerable and

reliable proof that peptide antigen-specific preventive therapy in animal models of experimental and spontaneous autoimmune disease is predictable (see Harrison and Hafler, supra). Applicants observe that, while the induction of specific tolerance might be "highly complex", operationally it is predictable, not unpredictable as asserted by the Examiner. It is firmly established that a peptide that stimulates T-cells, can be used to tolerize a subject. In fact, the inventors have determined that the proinsulin sequence of the present invention, while able to induce protective/regulatory CD4 + T-cells when administered intranasally, concomitantly induced potentially pathogenic cytotoxic CD8 + T-cells. However, the inventors also demonstrated that modifications of the peptide to disable the CTL epitope uncovered and enhanced the protective effect of the peptide when given intranasally. Thus, the inventors not only provide enabling support for the claimed peptide, but have also discovered a way of effectively modifying the peptide (see WO 01/30378 A1, Examples 10-12, attached as Exhibit B).

The Examiner further alleges that "it is not clear whether such immunotherapy can be used to treat an ongoing immune response (i.e. after the onset of symptoms, such as in IDDM) or whether it is effective only in terms of prevention." In response, Applicants respectfully direct the Examiner's attention to the data provided by the examples which fully support the practice of the claimed methods of treatment, without undue experimentation.

Accordingly, the rejection of claims 39, 40, 42 and 43 under 35 U.S.C. §112, first paragraph is overcome and withdrawal thereof is respectfully requested.

Claims 39 and 42 have been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. The Examiner alleges that it is "unclear how a sequence can consist of 15 residues and fall within the 13 amino acid stretch of amino acids 506 to 518 GAD 65 or the

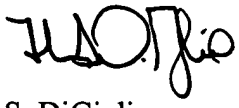
13 amino acid stretch of amino acids 24 to 36 of human proinsulin." In response, Applicants have amended claims 39 and 42 to recite that X_2 is any amino acid sequence from 10 to 13 residues derived from or contiguous within amino acids 506 to 518 inclusive of human GAD 65 or amino acids 24 to 36 inclusive of human proinsulin. Support for the amendments to claims 39 and 42 is found throughout the specification and particularly at page 3, lines 7-10, for example. No new matter has been added.

Claim 42 has been rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking descriptive support. In response, Applicants have amended claim 42 to delete the recitation "or derivative thereof", thus rendering the Examiner's rejection moot thereby. Withdrawal thereof is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"Version with Markings to Show Changes Made".**

Accordingly, in view of the foregoing amendments and remarks, the present application is deemed to be in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 39 has been amended as follows:

39.(Twice Amended) A recombinant or synthetic peptide consisting of the formula:

$$X_1\ X_2\ X_3$$

wherein X_1 and X_3 may be the same or different and each is an amino acid sequence consisting of from 0 to 40 naturally occurring amino acid residues; X_2 is any amino acid sequence of from 10 to [15] 13 residues derived from or contiguous within amino acids 506 to 518 inclusive of human GAD65 or amino acids 24 to 36 inclusive of human proinsulin; and wherein said peptide is capable of reacting with T cells and modifying T-cell function when incubated with cells from subjects with pre-clinical or clinical Insulin-Dependent Diabetes Mellitus (IDDM).

Claim 42 has been amended as follows:

42.(Twice Amended) A method of treatment comprising administering to a subject an effective amount of a peptide for a time and under conditions sufficient to remove or substantially reduce the presence in said subject of autoreactive T-cells or auto antibodies to IDDM autoantigens wherein the peptide consists of the formula:

$$X_1\ X_2\ X_3$$

wherein X_1 and X_3 may be the same or different and each is an amino acid sequence consisting of from 0 to 40 naturally occurring amino acid residues; X_2 is any amino acid sequence of from 10 to [15] 13 residues derived from or contiguous within amino acids 506 to 518 inclusive of human GAD65 or amino acids 24 to 36 inclusive [or derivatives thereof] of human proinsulin; and wherein said peptide is capable of reacting with T cells and modifying T-cell function when

incubated with cells from subjects with pre-clinical or clinical Insulin-Dependent Diabetes Mellitus (IDDM).